

THE REJECTION OF THE CLAIMS

Claims 1-11 are rejected under 35 USC 112 on the ground of indefiniteness in that the term used therein "NF- $\kappa$ B inhibiting amount" is not art recognized. Applicant begs to differ with the Examiner on this point. Anyone skilled in the art to which this specification refers knows how to determine an "NF- $\kappa$ B inhibiting amount" of a given drug by simply adding increasing dose levels of the drug until an inhibitory dosage is determined. Thus, the term will appear perfectly definite to those skilled in the art to which it pertains.

Applicant submits that the Examiner's objections to Claims 1-11 as indefinite have been overcome by the above amendments to said claims.

Claims 1-11 are rejected under 35 U.S.C. 103 over van't Riet et al on the ground that the compounds described in Claim 1 are known to be ribonucleotide inhibitors and free-radical scavengers. True. It is also true that anti-oxidants inhibit "activation of NF- $\kappa$ B". The error in the Examiner's rejection is in equating anti-oxidant activity which attacks the hydroperoxide free-radical itself which free-radical initiates a free-radical chain reaction, with free-radical scavenging activity which stops the chain reaction initiated by the peroxide. The anti-oxidants attack the free-radical reaction at its source; the free-radical scavengers stop the free-radical chain reaction once it has been started. Thus, antioxidant activity and free-radical scavenging activity are so distinct that one of ordinary skill in the art would never look to the antioxidant literature to find a free-radical scavenger.

In support of this position, Applicant is supplying two recent articles from SCIENCE, Salvemini et al 286 SCI 304 (1999) (BQ) and immediately following, Jenney et al ibid 306 (BR). Ref. BQ

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points out in the initial paragraph that superoxide dismutase (SOD) destroys the superoxide anion to give oxygen and hydrogenperoxide. The authors characterize the SOD enzymes as "oxidoreductases". Ref. BR discusses the reduction of superoxide to hydrogenperoxide and eventually water.

The difference between oxidation-reduction reactions and free radical reactions is that the former is invariably characterized by a change in valence (see Ref. BS , an excerpt from the Hogness & Johnson text) According to the reference, metals are good reducing agents since they tend to lose electrons (be reduced) whereas most non-metals tend to gain electrons (be oxidized). On the other hand, free-radical reactions are electronically neutral; ie, the initiator has a single free electron and the product of the reaction also has a single free electron so that the chain may be propagated. Thus, both starting material and product are electronically neutral.

Applicant's attorney in 1945 studied the decomposition of diacetyl peroxide in several alcohols. The results of these experiments are embodied in a publication by Kharasch et al appearing in the Journal of Organic Chemistry in 1951. (Ref. BT). Such free-radical chain reactions proceed until substrate is exhausted, or two free-radicals combine. Perhaps the difference between oxidation-reduction reactions and free-radical chain reactions can be illustrated by the chlorination of methane to produce methyl chloride.

$$\text{Cl}_2 \xrightarrow{h\nu} 2 \text{Cl}\cdot; \text{Cl}\cdot + \text{CH}_4 \rightarrow \text{CH}_3\text{Cl} + \text{H}\cdot; \text{H}\cdot + \text{Cl}_2 \rightarrow \text{HCl} + \text{Cl}\cdot$$
 where  $h\nu$  is a quantum of ultra violet light. These free-radical chains can terminate by the reaction of two methyl radicals to form methane or by the recombination of two chlorine atoms to form a chlorine molecule. The chain reaction can also be stopped by the addition of a chain-reaction terminator (a free-radical

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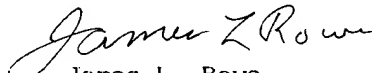
scavenger). While there would be little point in adding a free-radical scavenger to stop the chlorination of methane, in other free-radical chain reactions such as the reaction of styrene and butadiene to form Buna S rubber, addition of a chain terminator can control the degree of polymerization and hence the properties of the rubber polymer thus produced.

The above discussion and the cited references should indicate to the Examiner that reductive attack on the superoxide radical before it can initiate a chain reaction, and the use of a free-radical scavenger to terminate a chain reaction once propagated, are in such disparate fields of chemistry that no one seeking to terminate a chain reaction would look to the art relating to the reduction of the superoxide free-radical to find a suitable free-radical scavenger. Applicant's invention attacks the intracellular free-radical chain reaction begun by the activation of NF- $\kappa$ B, not the superoxide chain initiator. Applicant's point of attack on the process and the chemistry involved differ from the cited prior art processes and fundamental chemistry as set forth above. His invention would not be suggested thereby to one of ordinary skill in the art. Applicant submits that the rejection of the claims under 35 U.S.C. 103 has been overcome by the above arguments and should be withdrawn.

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It is believed that, with the above amendments to the specification and claims, there is no remaining bar to the allowance of Claims 1-3.5-7,& 9-13 remaining in the application. Favorable action thereon is respectfully requested.

Respectively submitted,

  
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